Association of cardiovascular risk factors with MRI indices of cerebrovascular structure and function and white matter hyperintensities in young adults

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Key Points

Questions: Are modifiable cardiovascular risk factors in young adults associated with cerebral blood vessel structure and function, and neuroimaging white matter hyperintensities?

Results: In this cross-sectional study of 125 young adults without clinical evidence of cerebrovascular disease, a higher number of optimal cardiovascular health metrics was correlated with higher cerebral vessel density, higher cerebral blood flow, and lower white matter hyperintensity lesions.

Meaning: These preliminary findings suggest a relationship between modifiable cardiovascular risk factors and MRI biomarkers of cerebrovascular structure and function and white matter hyperintensities in young adults. Further research is needed to verify these findings and determine clinical importance.

Abstract

Importance: Risk of stroke and brain atrophy in later life relate to levels of cardiovascular risk in early adulthood. However, it is unknown whether cerebrovascular changes are present in young adults.

Objective: To examine relationships between modifiable cardiovascular risk factors and cerebrovascular structure, function and white matter integrity in young adults.

Design, Setting, and Participants: A cross-sectional observational study of 125 young adults (aged 18 to 40 years) without clinical evidence of cerebrovascular disease with data collection completed between August 2014 and May 2016 at the University of Oxford, United Kingdom. Final data collection was completed on the 31st of May 2016.

Exposures: The number of modifiable cardiovascular risk factors at recommended levels, based on the following criteria: BMI <25 kg/m^2; highest tertile cardiovascular fitness and/or physical activity; alcohol <8 drinks/week; non-smoker for >6 months; blood pressure on awake ambulatory monitoring <130/80 mmHg; a non-hypertensive diastolic response to exercise (peak diastolic blood pressure <90 mmHg), total cholesterol <200mg/dL; and fasting glucose <100mg/dL. Participants were categorized from 0 to 8, with higher numbers indicating healthier risk categories.

Main Outcomes and Measures: Cerebral vessel density (vessels/cm^3), caliber (μm) and tortuosity, brain white matter hyperintensity lesion count (number), and in a subgroup (n=52) brain blood arrival time (seconds) and cerebral blood flow (ml/100g/min) assessed by brain magnetic resonance imaging.

Results A total of 125 participants, mean age 25±5 years, 49% female, with a mean score of 6.0 (SD 1.4) modifiable cardiovascular risk factors at recommended levels, completed the cardiovascular risk assessment and brain MRI protocol. Cardiovascular risk factors were correlated with cerebrovascular morphology and white matter hyperintensity count in multivariable models. For each additional modifiable risk factor categorized as healthy, vessel density was greater by 0.3 vessels/cm^3 (95%CI 0.1 to 0.5, p=0.003), vessel caliber was greater by 8μm (95%CI 3 to 13, p=0.01) and white matter hyperintensity lesions was lower by 1.6 lesions (95%CI 0.5 to 2.8, p=0.006). Among the 52 participants with available data, cerebral blood flow varied with vessel density and was 2.5ml/100g/min higher for each healthier category of a modifiable risk factor (95%CI 0.16 to 4.89, p=0.03).

Conclusions and Relevance In this preliminary study, involving young adults without clinical evidence of cerebrovascular disease, modifiable cardiovascular risk factors were associated with MR indices of cerebral vessel structure and function, and white matter hyperintensities. Further research is needed to verify these findings and determine clinical importance.

Key words: brain health, cardiovascular risk factors, young adults,

Introduction

A life-course approach to understand risk of cardiovascular disease is well established[1] and it is accepted that changes in cardiac and vascular structure that underlie this risk emerge very early in life[2, 3]. Whether modifiable cardiovascular risk factors, and novel early life exposures such as preterm birth, influence the early cerebrovasculature is less well studied.

Cardiovascular risk closely relates to cerebrovascular injury and cognitive decline in older adults[4]. MRI markers of cerebral injury in mid-life, including white matter hyperintensity lesions, are associated with future stroke, dementia and all-cause mortality[5]. Progression of white matter hyperintensity lesions is faster in association with metabolic dysfunction and hypertension[6]. Experimental studies have demonstrated that cardiovascular risk factors result in remodelling of the brain vasculature, including vessel rarefaction, lower vessel caliber and cerebral blood flow[7]. Elevated blood pressure, dyslipidemia and low fitness in early adulthood are known to predict brain health in older adult life[8-10]. Whether cerebrovascular morphological changes are already evident in young adults, and correlate with white matter hyperintensity lesions and risk factors at this age, is unclear.

Advances in brain MRI allow automated segmentation and analysis of vessel morphology, white matter hyperintensity lesions[11, 12] and blood flow[13]; thus making it possible to estimate brain vascular and structural status for an individual[11, 12]. Therefore, the objective of the current study was to use multi-modality brain imaging to test the hypothesis that cardiovascular risk profiles are correlated with variation in vessel morphology and white matter hyperintensity lesions in young adults.

Methods

Study design and participants

This was a cross-sectional observational study completed between August 2014 and May 2016. The South Central Research Ethics Committee for the National Health Service Health Research Authority (NHS HRA) approved the study (14/SC/0275). All participants gave written informed consent. Measurements were completed at the Oxford Cardiovascular Clinical Research Facility and Oxford Centre of Clinical Magnetic Resonance Research, John Radcliffe Hospital, University of Oxford, United Kingdom. Image analysis was performed using pipelines developed at the Hotchkiss Brain Institute, University of Calgary and Wellcome Centre for Integrative Neuroimaging, University of Oxford[12-16]. Final data collection was completed on the 31st of May 2016.

Participants aged 18 to 40 years were recruited through purposive active and passive recruitment[17] including local advertising, invitation from local birth cohort studies and invitation from the Oxford University Hospital Hypertension Service. Strategies were designed to recruit adults with a heterogeneity in risk factors known to be present in young adult populations including traditional risk factors such as hypertension and more novel factors such as gestational age. Participants were excluded if they had previous cardiovascular or cerebrovascular events, renal dysfunction or metabolic disease including diagnosis of familial hyperlipidaemia. Participants with secondary causes of hypertension such as renal vascular disease, vascular anomalies or adrenal dysfunction were excluded following assessment in Oxford University Hospital Hypertension Service.

Procedures

Cardiovascular Risk Assessment

Participants attended a research clinic in the morning after a 12-hour fast to complete a detailed cardiovascular risk assessment (Supplementary Data eMethods 1). Measurements included: body size, fasting blood samples for total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides, highly sensitive c-reactive protein, glucose, and insulin levels, clinic and 24-hour blood pressure, as well as peak oxygen uptake and exercise blood pressure (from cardiopulmonary exercise testing). In addition, participants completed a detailed lifestyle questionnaire and had seven complete days of objectively measured physical activity. Post-hoc, participants were assessed for a cardiovascular score based on 8 modifiable risk factors, with 1 point awarded for each healthier category of a modifiable risk factor according to the following criteria: BMI <25 kg/m^2; highest tertile cardiovascular fitness and/or physical activity; alcohol <8 drinks/week; non-smoker for >6 months; blood pressure on awake ambulatory monitoring <130/80 mmHg; a non-hypertensive diastolic response to exercise (peak diastolic blood pressure <90 mmHg), total cholesterol <200mg/dL; and fasting glucose <100mg/dL. The score was adapted from established cardiovascular health scores to include alcohol consumption and dynamic exercise blood pressure response, as known independent risk factors for brain health[19-21]. The thresholds for healthy criteria were set to be consistent with recommended public health guidelines and existing literature[4, 9, 18-20].

Brain Imaging and Analysis

Individuals underwent a multimodality MRI scan (3.0T Trio Tim, Siemens, Munich, Germany). The MRI protocol included T1-weighted structural, T2-weighted Fluid-Attenuated Inversion Recovery (FLAIR), Diffusion Tensor Imaging (DTI) and Time-of-Flight (TOF) MR Arteriogram (MRA) (Supplementary Data eMethods 2). MR imaging

was completed fasted and prior to exercise testing. Complete acquisition and analysis methods are presented in the on-line supplement.

T1-weighted images were processed using FMRIB Software Library (FSL) tools[21]. Brain vessel segmentation was completed on TOF MRA using previously described automated segmentation tools (supplement eFigure 1)[12, 16]. Binary segmentations were used to determine vessel density, caliber and tortuosity.

White matter hyperintensity (WMH) lesions and associated volumes were segmented using the Brain Intensity AbNormality Classification Algorithm (BIANCA); a fully-automated, supervised method for WMH detection[11, 22]. BIANCA classifies image voxels based on their intensity and spatial features, where the intensity features were extracted from T2-weighted FLAIR, T1-weighted and DTI fractional anisotropy (FA) images, FA images were generated using DTI tools, FSL topup, FSL eddy and DTIFit[21, 23]. WMH masks were manually segmented from 10 images to use as the training set for BIANCA, these were independently verified by a neurologist (TS) and radiologist (DM) blinded to participant risk profile. Lesion count was selected as the most sensitive outcome of white matter change in young adults in whom a single lesion, independent of volume, could be considered abnormal[24]. Minimum lesion size used in analysis was 1 mm^3.

A subgroup of 52 participants also had multi-delay vessel-encoded pseudocontinuous Arterial Spin Labelling (ASL), identical to a previously published protocol[13]. Cerebral blood flow and blood arrival time were estimated from ASL images using a previously described analysis pipeline[13, 15]. Gray matter masks were used to calculate the average cerebral blood flow after linear registration of the ASL MRI to the T1-weighted MRI dataset.

Statistical Analysis

Recruitment was continued to 125 participants for an estimated power of 90% at *P*=0.05 to identify a 0.70-SD difference in vessel density, vessel caliber and white matter lesion count between lowest and highest cardiovascular risk tertile groups. Arterial spin labelling (ASL) MRI imaging was added during the course of the study to provide a subgroup of 52 participants, recruited sequentially for an estimated 80% power to detect a 10% difference in cerebral blood flow[25].

Existing literature on risk predictors of brain health was used to define an a priori set of potential correlates of MRI brain health in young adults[4, 9, 18-20]. These were grouped as: 1) non-modifiable, including age, sex, gestational age, and 2) modifiable, including systolic blood pressure, body mass index (BMI), peak exercise capacity (oxygen uptake ml/min/kg), peak exercise diastolic blood pressure, weekly vigorous activity level, alcohol consumption, smoking history, lipid profile, glucose and insulin resistance, and current hypertension medication.

In a priori analysis, bivariable and multivariable analysis was completed to investigate correlation between the defined cardiovascular risk markers and brain imaging findings. In this multivariable analysis to reduce multiple testing and potential interaction between the variables, the model was restricted to a subset of variables (resting systolic blood pressure, BMI, vigorous physical activity level, alcohol consumption and smoking). This model was adjusted for non-modifiable factors including age, sex and gestational age.

In post-hoc analysis, the individuals' combined cardiovascular score from across 8 risk factors, was used as a metric of overall modifiable cardiovascular health. The relationships between the individuals' modifiable cardiovascular score and brain

imaging findings were studied using linear regression adjusted for age and sex. Comparison between brain imaging findings was made between groups of participants in the lowest and highest tertiles for the cardiovascular score.

In addition, bivariable analysis was completed to investigate correlation between vessel morphology and white matter hyperintensity lesion count and in a subgroup (n=52), blood arrival time and cerebral blood flow. These relationships were further investigated with fixed entry linear regression models adjusted for modifiable and non-modifiable factors used in the models above.

Statistical analysis was undertaken using Statistical Product and Service Solutions (SPSS) Version 22 (Armonk, New York, U.S). Normality of variables was assessed by visual assessment of curves. If normally distributed, results are presented as mean ± standard deviation for continuous variables, otherwise median and interquartile range. For categorical variables, number and percentage are presented. Comparison between groups for continuous variables was performed with a 2-sided, independent-sample Student's *t* test. All multivariable analysis was completed using forced entry linear regression with residual analysis completed to assess model assumptions. All multivariable analyses were adjusted for age and sex. All tests were 2-sided, P-values <0.05 were considered statistically significant with no adjustment for multiple comparison. Due to multiplicity of testing all results were considered exploratory. Results are presented as point estimates and 95% confidence intervals stated in units appropriate to the risk factor and brain imaging findings being reported. Graphpad Prism 7 software was used for statistical figures and mean with 95% confidence intervals presented.

Results

A total of 125 participants completed the brain MRI protocol and cardiovascular risk assessment study measures. The mean age of participants was 24.7±5.0 years, 61 participants were female (49%), the mean gestational age was 36.6±4.3 weeks, educational attainment was high with 86 completing University level education (68.8%), 29 participants had prior history of hypertension of which 21 were on anti-hypertension medications (16.8%) (Table 1). The distributions of MRI brain outcomes between lowest and highest quintile of the respective measures are presented in the supplement (eTable 1). The 52 participants with available cerebral blow flow data shared a comparable demographic profile as the overall study group (mean age 24.6 ±5.0 years, 42% female (n=22), gestational age 37.2±3.6 weeks, and 10 participants were on anti-hypertension medications (19.2%).

Modifiable risk factors and association with brain vessel structure and white matter hyperintensity lesions

Association between risk factors (SBP, BMI, smoking pack years, Ex DBP, cholesterol/HDL ratio, hypertension treatment) and brain vessel morphology are presented in Table 2. Vessel tortuosity only varied with gestational age in both bivariable and adjusted models (0.005 unit tortuosity change/gestational week, 95%CI 0.001 to 0.009, p=0.007) (Table 2 and Supplementary Data, eTable 2). In the multivariable models, systolic blood pressure (-0.2 vessels/cm^3 per 10mmHg, 95%CI -0.4 to -0.004, p=0.04), smoking (2 vessels/cm^3 per 10 pack years, 95%CI 0.6 to 3.0, p=0.04) and body mass index (-0.1 vessels/cm^3 per 1kg/m^2, 95%CI -0.15 to -0.01, p=0.02) were significantly correlated with vessel density, while vessel caliber was correlated with systolic blood pressure (-6μm per 10mmHg, 95%CI -10.0 to -0.5, p=0.03) and smoking (40μm per 10 pack years, 95%CI 2.0 to 80.0, p=0.04). In bivariable models, number of white matter hyperintensity lesions correlated with

smoking (8 lesions per 10 pack years, 95%CI 1.5 to 14.4, p=0.02), exercise diastolic blood pressure (1 lesions per 10mmHg, 95%CI 0.1 to 2.4, p=0.04), and alcohol consumption (4 lesion per 10 weekly alcoholic drinks, 95%CI 0.3 to 8.0, p=0.03), (Supplementary Data, eTable 3).

Healthier categories on the modifiable cardiovascular score correlated with vessel morphology (Table 4.) Each additional healthier category of risk factor was associated with a 0.3 vessels/cm^3 higher vessel density (95%CI 0.1 to 0.5, p=0.003) and 8μm greater vessel caliber (95%CI 3.0 to 13.0, p=0.01). Similarly, white matter hyperintensity lesion count correlated with the cardiovascular score with 1.6 fewer white matter hyperintensity lesions per additional healthier category of risk factor (95%CI to -3.0 to -0.5, p=0.006). In addition, the cardiovascular score correlated with total volume of white matter hyperintensity adjusted for brain size with 51 mm^3 lower white matter hyperintensity lesion volume per additional healthier category of risk factor (95%CI to -87 to -15 mm^3 p=0.006). Differences in vessel morphology and white matter hyperintensity lesions between tertiles of the study group, divided based on the cardiovascular score, are presented in Figure 1.

Vessel Morphology and brain MRI biomarkers of cerebral blood flow, arrival time and white matter lesion count

To explore whether cerebral blood flow also varied with cardiovascular risk factors, a subgroup (n=52) analysis was performed in those with cerebral blood flow measures (mean cerebral blood flow 60 ml/100g/min (SD 11.5) and mean blood arrival time 1.01 seconds (SD 0.08). Slower blood arrival time (0.1 seconds per 1kg/m^2, 95%CI 0.001 to 0.05, p=0.001) and lower cerebral blood flow (-1.1 ml/100g/min per 1kg/m^2, 95%CI -2.0 to -0.1, p=0.03) were correlated with higher BMI (Supplementary Data, eTable 3). Cerebral blood flow was also lower in correlation with anti-hypertensive medication 11 ml/100g/min (95%CI -18 to -3, p=0.007). Cerebral blood flow was

2.5ml/100g/min higher for each additional healthier category of the cardiovascular score (95%CI 0.16 to 4.89, p=0.03). There was no significant correlation between blood arrival time and the cardiovascular scores (Table 4).

In multivariable analysis, controlling for modifiable risk factors (SBP, BMI, VPA, smoking, alcohol intake) blood arrival time and cerebral blood flow varied with cerebral vessel density, with each additional vessel per cm^3 correlating with a 0.015 seconds faster blood arrival time (95%CI -0.03 to -0.002, p=0.02) and 3 ml/100g/min increase in cerebral blood flow (95%CI 0.7 to 5.4, p=0.01). Vessel density was inversely correlated with white matter hyperintensity lesion count with 1.5 fewer lesions per unit increase in vessel density per cm^3 (95%CI to -2.7 to -0.4, p=0.01). (Table 3).

Discussion

In this cross-sectional study, optimal status of modifiable cardiovascular risk factors in young adults were associated with differences in brain vessel structure and function as well as a lower number of white matter hyperintensity lesions. Higher vessel density correlated with both higher cerebral blood flow and lower white matter lesion counts.

To date, studies tracking changes in brain vascular measures have largely focused on the transition from middle age to older adulthood. Cerebral blood flow is estimated to decline over the life course[26] with risk of dementia in older adults being 2 to 3 fold higher in those whose cerebral blood flow is below 55 ml/100g/min[27]. Vascular dementia has also been associated with lower vascular density in brains of adults who have an early diagnoses of disease[28]. In the current study, young adults in the lowest tertile for the modifiable cardiovascular score had approximately 1 vessel/cm^3 lower vessel density and a mean value for cerebral blood flow of 55 ml/100g/min,

which is in the bottom 40% of the current study population. Therefore, the distribution of MRI findings observed in the current study raises the potential that some individuals may be starting to diverge on to different risk trajectories for brain vascular health in early adulthood. Furthermore, levels of cerebral blood flow associated with an increased risk of dementia are evident in some young adults. No participants had clinically significant white matter hyperintensity lesion volumes but lesion count was up to 4 lesions lower in the highest tertile of optimal status of modifiable risk factors.

Adverse modifiable cardiovascular risk factors are major determinants of white matter hyperintensity progression[29], with small lesions increasing in size or clustering into confluent lesions[30]. Accumulation of lesions from an early age might explain why, by mid-life, white matter hyperintensity lesion volume is an established predictor of future stroke and dementia risk[5]. The longitudinal relationships between vessel morphology, cerebral perfusion and white matter lesion burden are uncertain. However, the patterns observed in the current study may suggest that resilience of the white matter, and potential to withstand risk exposures, may be influenced by the vascular morphology of an individual.

Modifiable risk factors such as blood pressure, BMI, smoking and lipid profile are known to drive systemic vascular disease in young adults in part through biological vascular disorders including endothelial dysfunction and oxidative stress[31-33]. The current study suggests the cerebrovasculature may be similarly affected. Novel early life factors, such as preterm birth, are linked with early vascular disease[34] and the third trimester and early neonatal period are hypothesized to be times of significant vascular remodelling. In this study, gestational age was associated with vessel tortuosity, consistent with previous reports in infants[35], but not other cerebrovascular measures. Further work is needed to understand whether this was because

participants were largely born late preterm or because cardiovascular risk profile overwhelms this early exposure.[28].

The observed association between brain vascular measures and modifiable risk factors raises the potential for targeted intervention to prevent progression to disease. Reducing multiple risk factors can change risk trajectories and reduce vascular disease burden[36], with sustained lifestyle intervention and active blood pressure lowering associated with lower burden of white matter hyperintensity lesions and improved cerebral perfusion[37, 38]. These interventions typically achieve 25% improvements in cardiovascular fitness and 10 mmHg reductions in blood pressure[37, 38], comparable to differences between high and low tertile groups for the cardiovascular scores in this study.

However, lifestyle-based primary cardiovascular prevention in young adults requires complex intervention design. Recent systematic review of interventions in young hypertensives demonstrated that the optimal way to intervene is poorly understood with lack of sustained effect[39]. The alternative to lifestyle interventions would be pharmacological treatment. However, in this study group higher blood pressure was associated with reduced vessel density and anti-hypertensive use was associated with lower cerebral blood flow. Therefore, further work to identify optimal interventions in young adults to maintain autoregulation of cerebral blood flow, while reducing risk, may be required.

Limitations

This study has several limitations. First, a small sample recruited at a single site increases risk of bias and type 1 error while the study may be underpowered to identify subtle correlations with some risk factors. Second, purposive mixed passive and active recruitment strategies mean the sample is not population-based and could

be considered similar to a convenience sample. Therefore, it is not possible to generalise expected prevalence of cerebrovascular changes to the wider population. Third, the study is cross-sectional and causality or even temporality of the observed relationships cannot be inferred. Fourth, the cardiovascular risk assessment would be strengthened by detailed dietary questionnaires which were not included in this study. Fifth, cerebral blood flow was only available in a subgroup so ability to understand interactive effects of modifiable risk factors, vascular remodelling and perfusion on white matter integrity is limited. Sixth, longitudinal follow up will be required to determine the clinical significance of the observed findings. As such, this study should be considered preliminary and exploratory but does support a need for future work. The complexity of the imaging protocol and associated financial costs may limit its widespread use but large multi-centre studies with more focused protocols, and extended follow up, may have the potential to track vascular remodelling and assessment of impact on white matter and later disease.

Conclusion

In this preliminary study involving young adults without clinical evidence of cerebrovascular disease, modifiable cardiovascular risk factors were associated with MRI indices of cerebral vessel structure and function, and white matter hyperintensities. Further research is needed to verify these findings and determine clinical importance.

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Authorship

All authors meet criteria for authorship: WW, AJL, HB, CF, HD, PL contributed to the design of the study, secured funding and refined the overall study protocol and lead the project delivery, NF, LG, TO, MJ, CM contributed to the development of the Brain MRI protocol and related pipelines, AJL, WW, OH, JF, SN contributed to image acquisition and quality control, WW, NF, LG, TO, MJ, CM, JB, HB, TS, DM, RP contributed to brain MRI image processing and analysis, AD advised on accelerometer protocol for objective physical activity measurement and completed analysis of raw data, WW, AJL, HB, OH, completed cardiovascular risk assessment and analysis of measures, WW, CF, AJL, PL and EF contributed to the statistical analysis, WW wrote the manuscript with support from LG, OH, AJL, CF, NF, HD, PL. All authors contributed to revision of the manuscript. PL completed the final edit of the manuscript.

Disclosures

Dr. Okell reports grants from The Royal Academy of Engineering, during the conduct of the study; In addition, Dr. Okell has a patent (US Patent 9,757,047) with royalties paid from Siemens Healthcare. All other authors declare no competing interests.

Role of the funding source

The funders of the study had no role in design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Access to data

Dr. Williamson and Professor Leeson had full access to all of the data in the study and take full responsibility for the integrity of the data and the accuracy of the data analysis.

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591 Table **1. Age, demographics and cardiovascular risk profile of study group.**

	Study Group (n=125)
Demographics	
Age, mean (SD), years	24.7 (5.0)
Female, n, (%)	61 (49%)
Gestational Age, mean (SD), weeks	36.6 (4.3)
Smoking, n, (%)	19 (15.2)
Smokers' median pack years (Q1-Q3)	2.7 (6.7)
Alcohol, n, (%)	97 (77.6)
Alcohol consumers' median drinks per week (Q1-Q3)	4.0 (4.0)
Hypertension Diagnosis, n, (%)	29 (23.0)
Taking Hypertension Medication, n (%)	21 (16.8)
FHx Stroke or CHD, n, (%)	10 (8)
Education Level	
Completed University, n, (%)	86 (68.8)
Anthropometrics	
Height, mean (SD), m	1.73 (0.1)
Weight, mean (SD), kg	70.9 (13.8)
BMI, mean (SD), kg/m^2	23.6 (3.7)
Blood pressure, mean (SD), mmHg	
Resting Systolic	122.0 (11.6)
Resting Diastolic	71.3 (9.55)
Ambulatory Awake Systolic	129.6 (11.8)
Ambulatory Awake Diastolic	76.9 (8.0)
Peak Exercise Systolic	174.8 (25.4)
Peak Exercise Diastolic	87.1 (12.4)
Fitness	
Peak VO_2, mean (SD), ml/kg/min	37.9 (9.6)
Peak Respiratory Exchange Ratio, mean (SD)	1.2 (0.06)
VPA, median (Q1-Q3), hours per week	0.74 (1.25)
MVPA, median (Q1-Q3), hours per week	14.73 (6.09)
Biochemistry	
Total Cholesterol, mean (SD), mg/dL	170.15 (29.0)
LDL, mean (SD), mg/dL	97.45 (25.9)
HDL, mean (SD), mg/dL	55.68 (11.2)
TChol:HDL ratio, mean (SD)	3.18 (0.85)
Triglyceride, median (IQR), mg/dL	74.4 (54.0)
Blood Glucose, mean (SD), mg/dL	88.2 (7)
HOMA-IR, mean (SD)	0.77 (0.46)
HsCRP, median (Q1-Q3), mg/L	0.57 (1.16)
Brain MRI Vessel, Perfusion and White Matter Parameters	
Brain vessel density, mean (SD), $vessels/cm^3$	8.3 (1.41)
Brain vessel calibre, mean (SD), μm	531 (36)
Brain vessel tortuosity, mean (SD)	1.49 (0.088)
Brain white matter hyperintensity lesion count, mean (SD)	20.9 (7.9)
Brain Blood Arrival Time (SD), seconds	1.01 (0.08)
Cerebral Blood Flow (SD), ml/100g/min	60 (11.5)

592 Abbreviations: FHx, Family History, BMI, body mass index; SBP, systolic blood
593 pressure; DBP, diastolic blood pressure; Peak VO_2, Peak Oxygen Uptake; VPA,
594 Vigorous Physical Activity; MVPA, Moderate to Vigorous Physical Activity; LDL, low
595 density lipoprotein; HDL, high density lipoprotein; T Chol: total cholesterol; HsCRP,
596 highly sensitive C reactive protein; HOMA-IR, homeostatic model assessment of

insulin resistance. Brain blood arrival time and cerebral blood flow data was available in 52 participants.

Table 2. Association between non-modifiable and modifiable risk factors and brain vessel morphology (vessel density, caliber and tortuosity).

	Bivariable Point Estimate (95 %CI)	P value	Adjusted Point Estimate (95 %CI)	P value
Brain Vessel Density (vessels/cm^3)			**Model Statistics R^2=0.20 p =.009**	
Gestational Age, weeks	-0.001 (-0.06 to 0.06)	.98	-0.02 (-0.08 to 0.03)	.42
Resting SBP, mmHg	-0.03 (-0.05 to -0.004)	**.02**	-0.02 (-0.04 to -0.0004)	**.046**
BMI, kg/m^2	-0.10 (-0.16 to -0.02)	**.01**	-0.08 (-0.15 to -0.01)	**.02**
VPA, hours per week	0.10 (-0.17 to 0.39)	.42	-0.04 (-0.28 to 0.20)	.75
Alcoholic drinks per week	-0.10 (-0.025 to -0.008)	.31	-0.01 (-0.04 to 0.02)	.41
Smoking pack years	0.20 (0.06 to 0.30)	**.004**	0.17(0.06 to 0.28)	**.004**
Peak VO_2, ml/kg/min	0.01 (-0.02 to 0.04)	.5	.	.
Peak Ex DBP, mmHg	-0.02 (-0.04 to -0.003)	**.047**	.	.
Cholesterol/HDL Ratio	-0.40 (-0.69 to -0.06)	**.02**	.	.
HOMA IR	-0.56 (-1.17 to 0.04)	.07	.	.
Hypertension Rx	0.75 (-0.01 to 1.5)	.05	.	.
Brain Vessel Caliber (μm)			**Model Statistics R^2=0.24 p=.001**	
Gestational Age, weeks	-0.1 (-2.0 to 1.0)	.88	-1.0 (-3.0 to 0.5)	.16
Resting SBP, mmHg	-0.4 (-1.0 to 2.0)	.15	-0.6 (-1.0 to -0.05)	**.03**
BMI, kg/m^2	-1.0 (-3.0 to 1.0)	.33	-1.0 (-3.0 to 1.0)	.42
VPA, hours per week	1.0 (-6.0 to 8.0)	.73	-2.0 (-9.0 to 4.0)	.49
Alcoholic drinks per week	-0.1 (-1.0 to 1.0)	.70	-1.0 (-2.0 to 0.1)	.09
Smoking pack years	3.0 (-0.2 to 6.0)	.06	4.0 (0.2 to 8.0)	**.04**
Peak VO_2, ml/kg/min	0.4 (-0.2 to 1.0)	.19	.	.
Peak Ex DBP, mmHg	-1.0 (-1.4 to -0.4)	**<.001**	.	.
Cholesterol/HDL Ratio	-3.0 (-10.0 to 5.0)	.52	.	.
HOMA IR	-14.0 (-30 to 1.0)	.08	.	.
Hypertension Rx	10 (-9.0 to 31.0)	.27	.	.
Brain Vessel Tortuosity			**Model Statistics R^2=0.1 p=.26**	
Gestational Age, weeks	0.005 (0.001 to 0.009)	**.007**	0.006 (0.001 to 0.01)	**.01**

Also modelled was the association between these risk factors and tortuosity, and only gestational age was related, full analysis presented in supplement (eTable 1). Model adjusted for non-modifiable factors of age, sex, gestational age and modifiable risk factors of systolic blood pressure, body mass index, vigorous physical activity, weekly alcohol consumption and smoking status. Abbreviations and units: SBP, systolic blood pressure (mmHg); BMI, body mass index (kg/m^2); VPA, Vigorous Physical Activity (hours per week); Alcohol (drinks per week); Smoking (pack years); Peak VO_2, Peak Oxygen Uptake (ml/kg/min); Ex DBP, Peak exercise diastolic blood pressure (mmHg), Cholesterol/HDL ratio, ratio total cholesterol/high density lipoprotein; HOMA-IR, homeostatic model assessment of insulin resistance,

613 Hypertension Rx participant taking prescription medications for hypertension
614 (yes/no)**.** Exposure variables were available for all participants. The point estimate
615 refers to the magnitude of change in the vessel morphology variable per unit change
616 in the non-modifiable and modifiable variables.

617

Table 3. Association of vessel morphology (density, caliber, tortuosity) with measures of brain blood arrival time, cerebral blood flow and white matter hyper-intensity lesions

	Bivariable Point Estimate (95 %CI)	P Value	Adjusted Point Estimate (95 %CI)	P Value
Blood Arrival Time (seconds) (n=52)				
Brain Vessel Density, vessels/cm^3	-0.03 (-0.04 to -0.01)	**.002**	-0.015 (-0.03 to -0.002)	**.02**
Brain Vessel Caliber, µm	0.08 (-0.61 to 0.78)	.81	0.22 (-0.28 to 0.71)	.38
Brain Vessel Tortuosity	0.13 (-0.15 to 0.4)	0.36	-0.014 (-0.23 to 0.21)	.90
Cerebral Blood Flow (ml/100g/min) (n=52)				
Brain Vessel Density, vessels/cm^3	4.0 (1.8 to 6.2)	**.001**	3.1 (0.7 to 5.4)	**.01**
Brain Vessel Caliber, µm	48.6 (-50.3 to 147.6)	.34	-8.0 (-126.1 to 110.1)	.89
Brain Vessel Tortuosity	3.8 (-36.4 to 44.1)	.85	12.9 (-35.4 to 61.1)	.60
White Matter Hyperintensity Lesion Count (lesions) (n=125)				
Brain Vessel Density, vessels/cm^3	-1.1 (-2.2 to 0.06)	.06	-1.5 (-2.7 to -0.4)	**.01**
Brain Vessel Caliber, µm	13.5 (-31.3 to 58.4)	.55	12.1 (-34.5 to 57.8)	.61
Brain Vessel Tortuosity	-17.5(-35.3 to 0.24)	.05	-11.0 (-29.0 to 7.0)	.23

Model adjusted for non-modifiable factors of age, sex, gestational age and modifiable risk factors of systolic blood pressure, body mass index, vigorous physical activity, weekly alcohol consumption and smoking status. Also modelled were the association with vessel caliber and tortuosity, only vessel density was related. The point estimate refers to the magnitude of change in blood arrival time, cerebral blood flow or number of white matter hyperintensity lesions per unit change in respective vessel morphological variable.

Table 4. Modifiable cardiovascular score and association with brain vessel morphology, cerebral blood flow and white matter hyperintensity lesion count

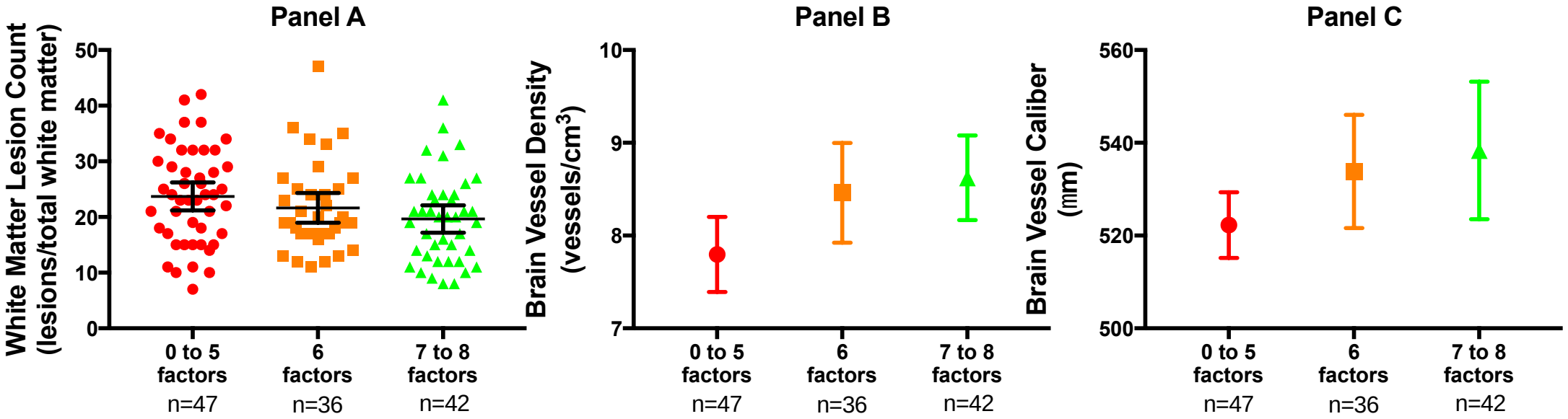
Modifiable Cardiovascular Score	**Brain Vessel Density, vessels/cm^3** point estimate (95%CI)	**Brain Vessel Caliber, µm** point estimate (95%CI)	**Brain Vessel Tortuosity** point estimate (95%CI)	**Brain Blood Arrival Time, seconds (n=52)** point estimate (95%CI)	**Cerebral Blood Flow, ml/min/100g (n=52)** point estimate (95%CI)	**Brain white matter hyperintensity lesion count, number** point estimate (95%CI)
1 (n=2)	9.2 (6.4 to 11.9)	505 (437 to 573)	1.52 (1.44 to 1.50)	.	.	36.2 (24.3 to 48.0)
2 (n=0)	.	.	.	.	.	.
3 (n=4)	6.9 (5.0 to 8.8)	518 (470 to 565)	1.49 (1.46 to 1.52)	1.26 (1.16 to 1.36)	66.6 (50.4 to 82.0)	24.0 (16 to 32)
4 (n=14)	7.4 (6.6 to 8.2)	512 (493 to 532)	1.47 (1.45 to 1.53)	1.22 (1.16 to 1.27)	54.2 (45.5 to 63.0)	25.0 (21.0 to 29.2)
5 (n=27)	8.0 (7.4 to 8.5)	524 (510 to 540)	1.51 (1.47 to 1.55)	1.21 (1.16 to 1.26)	54.6 (47.0 to 62.0)	22 (19.0 to 25.3)
6 (n=36)	8.5 (8.0 to 9.0)	533 (521 to 545)	1.49 (1.46 to 1.52)	1.19 (1.15 to 1.23)	60.2 (54.0 to 67.0)	21.0 (19.0 to 24.0)
7 (n=33)	8.5 (8.0 to 9.0)	542 (530 to 555)	1.48 (1.45 to 1.52)	1.18 (1.14 to 1.22)	64.0 (57.8 to 70.0)	19.0 (16.2 to 21.8)
8 (n=9)	9.1 (8.2 to 10.0)	540 (518 to 563)	1.54 (1.46 to 1.62)	1.18 (1.11 to 1.24)	68.0 (57.6 to 78.1)	20.0 (15.4 to 26.6)
Change in point estimate per additional score (n=125)	0.31 (0.112 to 0.514)	8.0 (3.0 to 13.0)	0.005 (-0.008 to 0.18)	-0.014 (-0.03 to 0.001)	2.5 (0.16 to 4.89)	-1.6 (-3.0 to -0.5)

Participants were assessed for a cardiovascular score, for each healthier category of a modifiable risk factor according to the following criteria: BMI <25 kg/m^2; highest tertile cardiovascular fitness and/or physical activity; alcohol <8 drinks/week; non-smoker for >6 months; blood pressure on awake ambulatory monitoring <130/80 mmHg; a non-hypertensive diastolic response to exercise (peak diastolic blood pressure <90 mmHg), total cholesterol <200mg/dL; and fasting glucose <100mg/dL. Adjusted for age and sex. The point estimate refers to the magnitude of change in the dependent variable per unit change in the modifiable cardiovascular score.

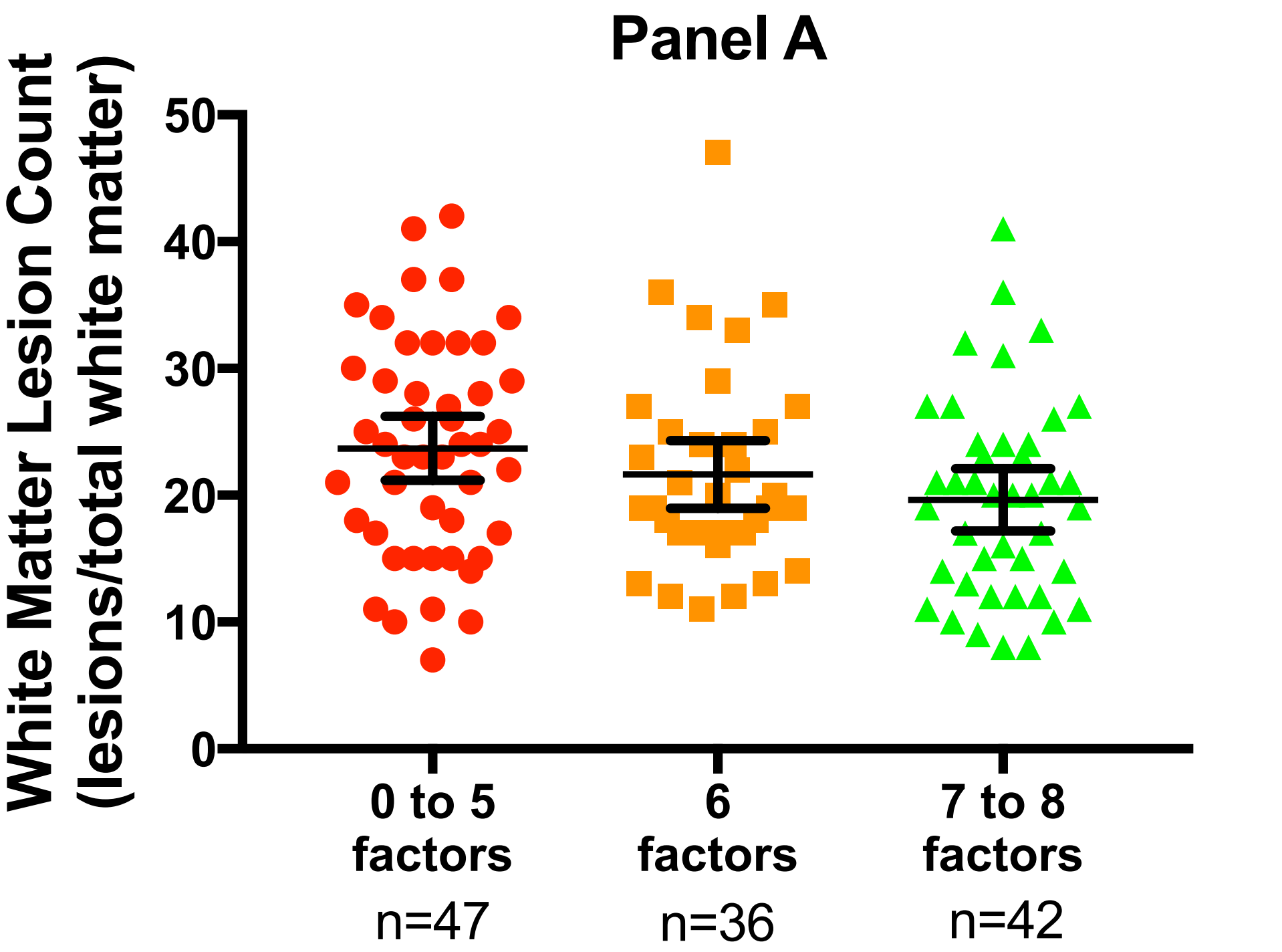
Figure 1. Comparison of white matter lesion count and vessel morphology between groups of participants based on their modifiable cardiovascular score.

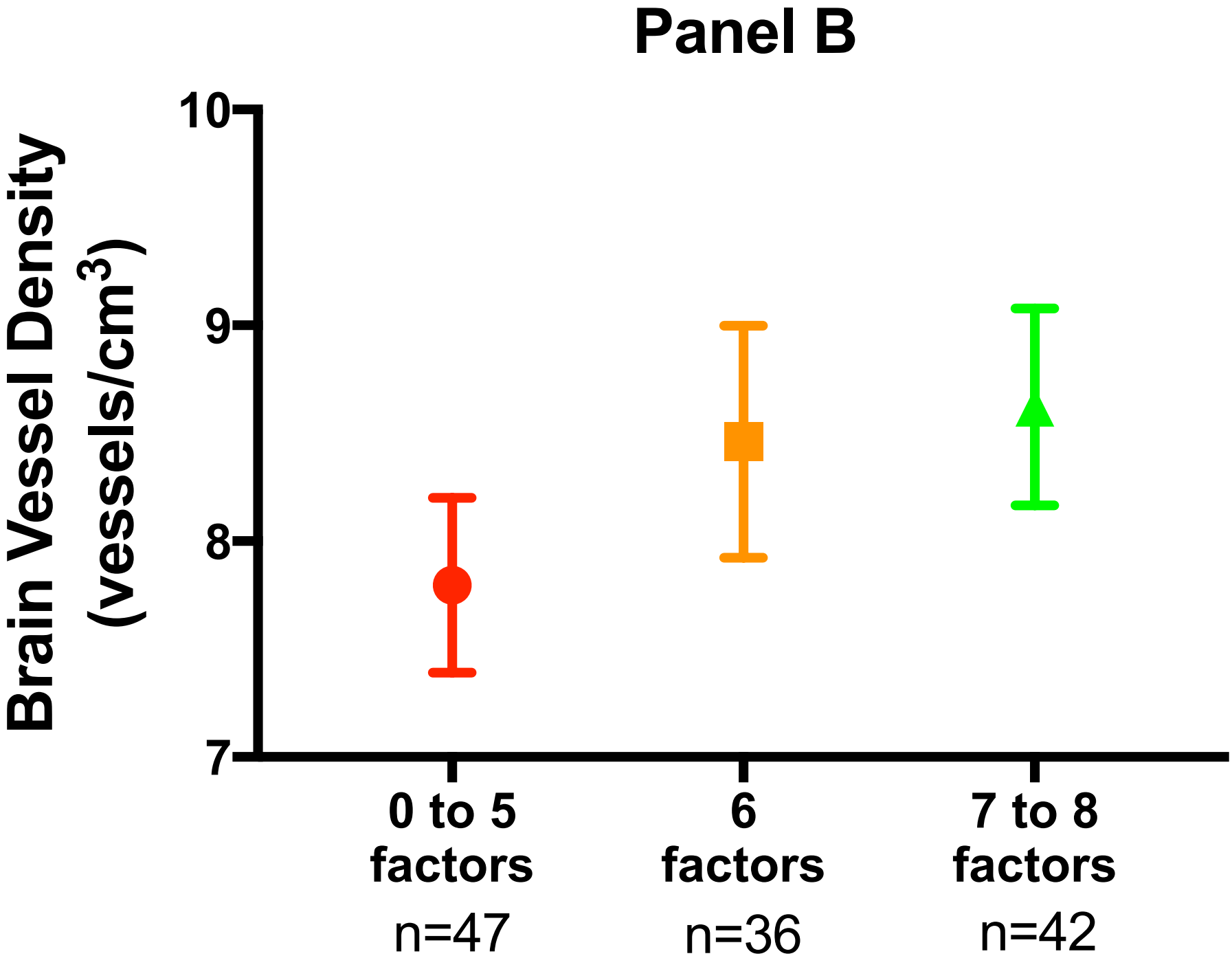
The cardiovascular score provided a cumulative score for each of the following factors: high cardiovascular fitness (top tertile of peak oxygen uptake (>=110% predicted peak oxygen uptake) or participating in >=75 minutes vigorous physical activity per week); not smoking in last 6 months; alcohol <8 drinks/week; ambulatory awake blood pressure <130/80mmHg; body mass index <25kg/m^2; fasting total cholesterol <200 mg/d; fasting blood glucose <100 mg/dL; and diastolic blood pressure at peak exercise <= 90mmHg. Figure 1 presents a post-hoc comparisons between groups of participants who score 0 to 5 positive factors (n=47), 6 factors (n=36) and 7 to 8 positive factors (n=42). The groupings were defined to approximate tertiles of the combined cardiovascular score. Panel A presents the white matter lesions counts for individual participants and associated group mean and 95% CI, Panels B and C present the mean group values and 95% CI. Participants with 7 to 8 healthier categories of risk factor have a mean vessel density 11% higher than participants with 0 to 5 healthier categories of risk factor (Panel B, 8.6 vessels/cm^3 (SD 1.39) vs 7.8 vessels/cm^3 (SD 1.21) p=0.007), a mean vessel caliber 3% higher (Panel C, 538μm (SD 21) vs 522μm (SD 45) p=0.02) and on average 20% lower white matter hyperintensity lesion counts (Panel A, 19.6 lesions (SD 7.8) vs 23.5 lesions (SD 8.6) p=0.03). Panels present group means and 95%CI and reported group differences are adjusted for age and sex.

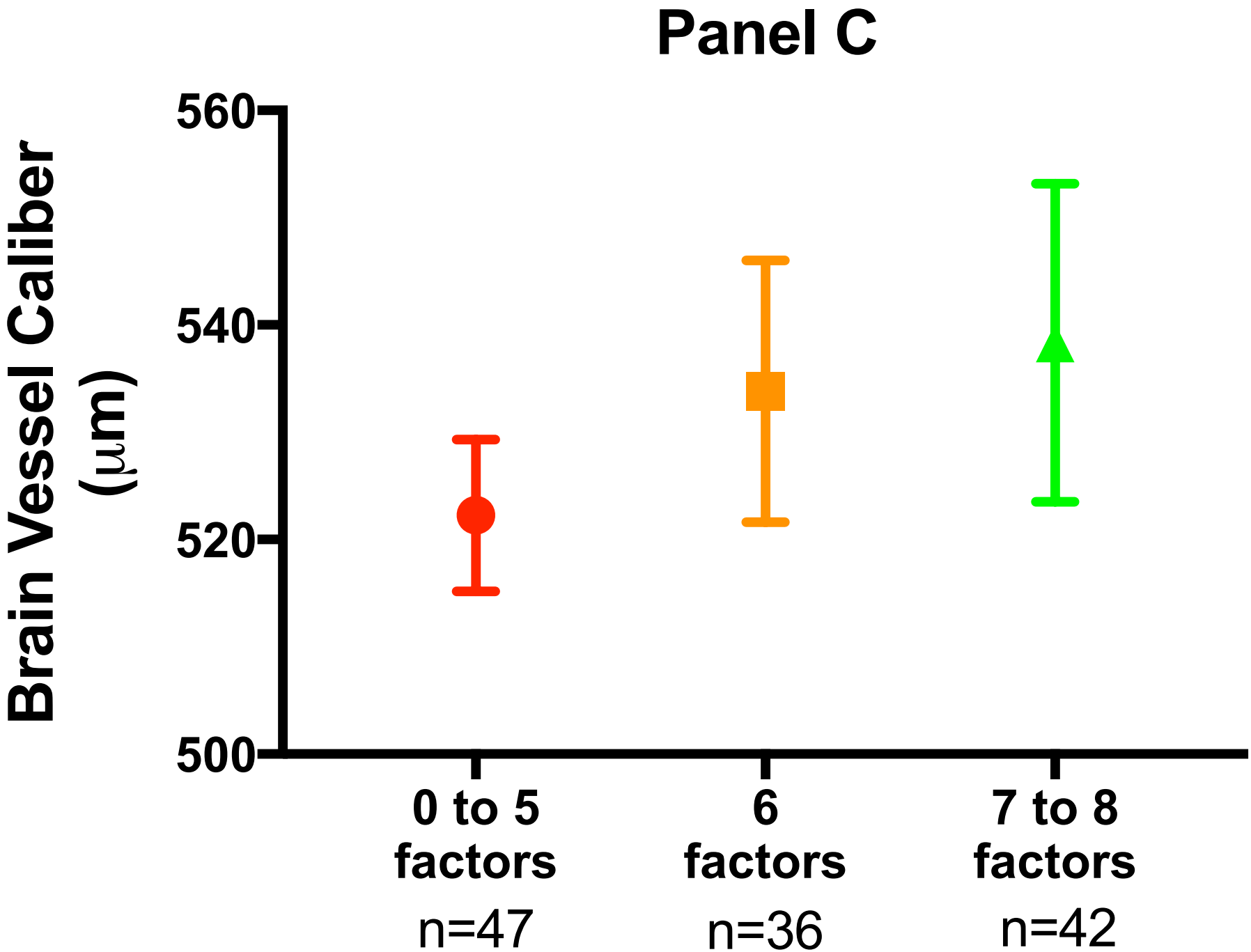
Figure 1. Comparison of white matter lesion count and vessel morphology between groups of participants based on their modifiable cardiovascular score.



The cardiovascular score provided a cumulative score for each of the following factors: high cardiovascular fitness (top tertile of peak oxygen uptake (>=110% predicted peak oxygen uptake) or participating in >=75 minutes vigorous physical activity per week); not smoking in last 6 months; alcohol <8 drinks/week; ambulatory awake blood pressure <130/80mmHg; body mass index <25kg/m^2; fasting total cholesterol <200 mg/d; fasting blood glucose <100 mg/dL; and diastolic blood pressure at peak exercise <= 90mmHg. Figure 1 presents a post-hoc comparisons between groups of participants who score 0 to 5 positive factors (n=47), 6 factors (n=36) and 7 to 8 positive factors (n=42). The groupings were defined to approximate tertiles of the combined cardiovascular score. Panel A presents the white matter lesions counts for individual participants and associated group mean and 95% CI, Panels B and C present the mean group values and 95% CI. Participants with 7 to 8 healthier categories of risk factor have a mean vessel density 11% higher than participants with 0 to 5 healthier categories of risk factor (Panel B, 8.6 vessels/cm^3 (SD 1.39) vs 7.8 vessels/cm^3 (SD 1.21) p=0.007), a mean vessel caliber 3% higher (Panel C, 538µm (SD 21) vs 522µm (SD 45) p=0.02) and on average 20% lower white matter hyperintensity lesion counts (Panel A, 19.6 lesions (SD 7.8) vs 23.5 lesions (SD 8.6) p=0.03). Panels present group means and 95%CI and reported group differences are adjusted for age and sex.


Panel A
White Matter Lesion Count
(lesions/total white matter)
50
40
30
20
10
0
0 to 5
factors
n=47
6
factors
n=36
7 to 8
factors
n=42


Panel B
Brain Vessel Density
(vessels/cm3)
10
9
8
7
0 to 5
factors
n=47
6
factors
n=36
7 to 8
factors
n=42


Panel C
Brain Vessel Caliber (μm)
560
540
520
500
0 to 5 factors
n=47
6 factors
n=36
7 to 8 factors
n=42